Table 26-3 Subtypes of Osteogenesis Imperfecta

Subtype	Collagen Defect	Inheritance	Major Clinical Features	Prognosis
I	Decreased synthesis of pro-α1(1) chain Abnormal pro-α1(1) or pro-α2(1) chains	Autosomal dominant	Postnatal fractures, blue sclera Normal stature Skeletal fragility Dentinogenesis imperfecta Hearing impairment Joint laxity Blue sclerae	Compatible with survival
II	Abnormally short pro-α1(1) chain Unstable triple helix Abnormal or insufficient pro-α2(1)	Most autosomal recessive Some autosomal dominant New mutations	Death in utero or within days of birth Skeletal deformity with excessive fragility and multiple fractures Blue sclera	Perinatal lethal
III	Altered structure of pro-peptides of pro-α2(1) Impaired formation of triple helix	Autosomal dominant (75%) Autosomal recessive (25%)	Compatible with survival Growth retardation Multiple fractures Progressive kyphoscoliosis Blue sclera at birth that become white Hearing impairment Dentinogenesis imperfecta	Progressive, deforming
IV	Short pro-α2(1) chain Unstable triple helix	Autosomal dominant	Postnatal fractures, normal sclerae Moderate skeletal fragility Short stature Sometimes dentinogenesis imperfecta	Compatible with survival

OI, Osteogenesis imperfecta.

in the zone of proliferation. It is also caused by gain-of-function mutations in FGFR3 that differ from those in achondroplasia.

Abnormal bone density can result from mutations in genes that regulate osteoclast differentiation or osteoclast function. Such mutations can cause either osteoporosis (too little bone) or osteopetrosis (too much), which are described in more detail in separate sections. Interestingly, specific mutations in the gene for the receptor *LPR5* can manifest as either osteoporosis or osteopetrosis in adults, depending on the gene defect. One infantile form of osteopetrosis is associated with mutation of *RANKL,* resulting in decreased or absent osteoclasts. In animals, osteopetrosis can also be caused by mutations in *M-CSF* and *OPG*, which (as already discussed) regulate osteoclast formation and function.

Defects in Extracellular Structural Proteins

The interaction of the organic components of bone matrix is complex and a focus of intense scientific investigation. The importance of the structural bone proteins is exemplified by the diseases associated with deranged metabolism of the major bone and cartilage collagens (types I, II, IX, X, and XI). Their clinical manifestations are highly variable, ranging from lethal disease to premature osteoarthritis.

Type I Collagen Diseases (Osteogenesis Imperfecta)

Osteogenesis imperfecta (OI), or brittle bone disease, is a phenotypically diverse disorder caused by deficiencies in the synthesis of type I collagen. It is the most common inherited disorder of connective tissue. OI principally affects bone, but also impacts other tissues rich in type I collagen (joints, eyes, ears, skin, and teeth). It usually results from autosomal dominant mutations (more than 800 have been identified) in the genes that encode the α1 and α2 chains of type I collagen. Many of these mutations lead to replacement of a glycine residue with another amino acid in the triple-helical domain, resulting in defective assembly of higher order collagen polypeptides. Collagen synthesis and extracellular transport require triple helix formation, and these defects not only cause the misfolding of the mutated collagen polypeptides, but also interfere with the proper assembly of wild type collagen chains (a dominant negative loss of function activity).

The fundamental abnormality in OI is too little bone, resulting in extreme skeletal fragility. Other findings include blue sclerae caused by decreased collagen content, making the sclera translucent and allowing partial visualization of the underlying choroid; hearing loss related to both a sensorineural deficit and impeded conduction due to abnormalities in the bones of the middle and inner ear; and dental imperfections (small, misshapen, and blue-yellow teeth) secondary to a deficiency in dentin.

Osteogenesis imperfecta can be separated into four major clinical subtypes that vary widely in severity (Table 26-3). The severity of the disease is based on the location of the mutation within the protein. Mutations resulting in decreased synthesis of qualitatively normal collagen are associated with mild skeletal abnormalities. More severe or lethal phenotypes have abnormal polypeptide chains that cannot be arranged in a triple helix. The type 2 variant is at one end of the spectrum and is uniformly fatal in utero or during the perinatal period. It is characterized by extraordinary bone fragility with multiple intrauterine fractures (Fig. 26-6). In contrast, individuals with the type 1 form have a normal life span but experience childhood fractures that decrease in frequency following puberty.

Diseases Associated with Mutations of Types II, IX, X, and XI Collagen

Types II, IX, X, and XI collagens are important structural components of hyaline cartilage. Although uncommon, mutations in the genes encoding these proteins produce an